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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/664,667	09/18/2003	Wei Gu	MPI99-037P1RCP1CN1M	5794

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MILLENNIUM PHARMACEUTICALS, INC.
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EXAMINER
LI, RUIXIANG

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 06/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/664,667	GU, WEI	
	Examiner	Art Unit	
	Ruixiang Li	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09/18/2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *09/18/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicants' election of Group I (Claims 1-7, 12, 18) in a reply filed on 04/05/2005 is acknowledged. Applicants' election with traverse of a nucleotide sequence encoding a polypeptide of SEQ ID NO: 5 is also acknowledged. The traverse is on the ground that each of the sequences SEQ ID NOS: 4, 6, 7, 9, 10, and 12 encodes partial or full length human LGR6, and as such, a search of one group would include a search of other groups. Applicants submit that joinder of these sequences would place no additional burden on the Examiner. This has been fully considered but is not deemed to be persuasive because the three amino acid sequences SEQ ID NOS: 5, 8, and 11, and their encoding nucleic acid sequences do not appear to relate to each other merely as "partial" and "full" sequences. Each of the three amino acid sequences represents a structurally and functionally distinct entity that is capable of supporting a separate patent. Thus, search and consideration of all of the sequences constitutes an undue search burden on the office, given the ever-increasing size of the database.

   The requirement is still deemed proper and is therefore made FINAL.

2. Applicants' amendment in a reply filed on 04/05/2005 has been entered in full. Claims 1-22 have been canceled. New claims 23-40 have been added. Claims

23-40, drawn to a nucleotide encoding the amino acid sequence of SEQ ID NO: 5, are under consideration.

Information Disclosure Statement

3. The information disclosure statement filed on 09/18/2003 has been considered by the examiner.

Drawings

4. The drawings filed on 09/18/2003 are accepted by the Examiner.

Objections to Disclosure

5. The disclosure is objected to because of the following informalities:

(i). It contains an embedded hyperlink (see, e.g., page 23, lines 16 and 20). Applicant is required to delete the embedded hyperlink. See MPEP § 608.01.

(ii). The disclosure is objected to because ATCC deposit accession number and the data are missing (e.g., pages 3, 5-7). If the deposit is not going to be made, reference to the deposit should be deleted from the specification. If the deposit has been made, the specification should be amended accordingly. If the deposit has not been completed, Applicants should advise in the next response. However, the objection will be maintained until either the specification is amended or reference to the deposit is deleted.

Appropriate correction is required.

Rejections—35 USC § 101

6. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claims 23-40 are rejected under 35 U.S.C. §101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

Claims 23-40 are drawn to an isolated nucleic acid molecule comprising SEQ ID NO: 4 or 6, or a nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 5, an expression vector, a host cell, and a method of producing a polypeptide. The claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. A specific and substantial utility is one that is particular to the subject matter claimed and that identifies a "real world" context of use for the claimed invention which does not require further research.

The instant specification discloses the polypeptide of SEQ ID NO: 5 (or LGR6) and its encoding nucleic acids of SEQ ID NO: 4 and 6, as well as the tissue distribution of LGR6 mRNA (Example 2). Nonetheless, the instant disclosure fails to provide any sufficient information or evidence on the specific biological functions or physiological significance of the molecules of the present invention and fails to disclose a patentable utility for the claimed invention.

First, the invention lacks a well-established utility. A well-established utility is a specific, substantial, and creditable utility that is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material. The sequence and prior art search does not reveal that the polypeptide of SEQ ID NO: 4 or the nucleic acid encoding the polypeptide has any well-established biological functions or any physiological significance. While asserting that the polypeptide of SEQ ID NO: 4 is a member of the G-protein coupled receptor family (lines 9-11 of page 3), possesses certain domains, and have certain signal transduction activities of GPCR family (see, page 9), the instant disclosure fail to provide sufficient information, showing that the LGR6 polypeptide of the present invention has a defined biological function. Since there is no single common biological function for members of GPCR family, the homology of the LGR6 with members of GPCR family does not render the claimed invention a specific biological function and thus a specific and substantial utility. Moreover, the state of the art is such that the biological functions of proteins are unpredictable solely based upon sequence homology. In view of the diversity of the biological functions of the GPCR proteins, as acknowledged in the instant disclosure (pages 1-3 of the specification), prediction of function using comparative sequence analysis may lead to the creation and propagation of assignment errors if not performed appropriately (See, Peer Bork and Eugene V. Koonin, Predicting functions from protein sequences--where are the bottlenecks? *Nature Genetics* 18:313-318,1998). No art of record discloses or suggests

any property or activity for the claimed molecules such that another non-asserted utility would be well-established for the claimed invention.

Secondly, the present invention does not disclose a specific and substantial utility. The specification asserts that the LGR6 nucleic acid and protein molecules of the present invention are useful as targets for developing modulating agents that regulate a variety of cellular processes (lines 11-14 of page 3) and that nucleic acids of the present invention can be used as primers or hybridization probes for detection of LGR6-encoding nucleic acids (lines 15-17 of page 3). The specification also asserts that the molecules (nucleic acids, polypeptides, proteins homologues, antibodies) can be used in screening assays (page 85), and detection assays (page 93), e.g., chromosomal mapping (page 93), and tissue typing (page 95). However, such uses are all considered research uses only designed to identify a particular function of the molecules of the present invention and are not a substantial utility. See, e.g., *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966) wherein a research utility was not considered a "substantial utility." Moreover, such uses are not specific to the instant molecule, but rather applicable to any nucleic acids or proteins.

The instant specification also asserts that the polypeptide of SEQ ID NO: 4 have numerous signal transduction activities of GPCR family (see, page 9). The asserted utility is not substantial because obviously further research is required to establish the specific biological function of LGR6. The specification further asserts that the molecules of the present invention can also be used

in predictive medicine (page 97) and are useful for the diagnosis and treatment of a disorder associated with a misregulation in LGR6 protein activity or nucleic acid expression, such as a weight, cardiovascular, neural or endocrine disorder (pages 97, 98, and 100). These asserted utilities are not specific and substantial because they do not identify or reasonably confirm a "real world" context of use. The disclosure neither identifies the biological functions of the LGR6 nucleic acid nor any specific disorders that are associated with the LGR6 nucleic acid. Clearly, further research would be required to determine the functions of the claimed molecules or to identify a specific disease that can be treated or diagnosed with the claimed molecules. See *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966), noting that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."

Accordingly, the claimed invention is not supported by a specific and substantial asserted utility or a well-established utility.

8. Claims 23-40 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Furthermore, even if the nucleic acid encoding the polypeptide of SEQ ID NO: 5 were to have a patentable utility, the instant disclosure would not be found to be enabling for the full scope of the invention of claims 38-40.

The factors that are considered when determining whether a disclosure satisfies enablement requirement include: (i) the quantity of experimentation necessary; (ii) the amount of direction or guidance presented; (iii) the existence of working examples; (iv) the nature of the invention; (v) the state of the prior art; (vi) the relative skill of those in the art; (vii) the predictability or unpredictability of the art; and (viii) the breadth of the claims. *Ex Parte Forman*, 230 USPQ 546 (Bd Pat. App. & Int. 1986); *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Claims 38-40 are drawn to a kit comprising a compound which selectively hybridizes to a nucleic acid molecule encoding the amino acid sequence of SEQ ID NO: 5. Since there is no structural limitation for the compounds, the genus encompasses any compounds, not just nucleic acids, which hybridize or binds to the nucleic acid of the present invention. Moreover, since claims have no recitation of specific hybridization conditions and any nucleic acids could hybridize to the nucleic acid sequence recited in the claims, the claims encompass virtually any random nucleic acid sequence of any length. For example, the claims read on a nucleic acid molecule comprising a fragment of the nucleic acid encoding SEQ ID NO: 5, a variant of the nucleic acid sequence encoding SEQ ID NO: 5 that does not have the same activity as that of the nucleic acid encoding the SEQ ID NO: 5. Thus, the claims are remarkably broad and encompass an enormous genus of compounds.

However, other than the nucleic acid molecules of SEQ ID NO: 4 and 6

that encode the amino acid sequence of SEQ ID NO: 5, the instant disclosure fails to provide sufficient direction or working example on how to make and use the claimed compounds. There is no specific disclosure of the compounds other than nucleic acids. With respect to nucleic acids, the specification is silent with respect to which residues may be altered without loss of activity. The instant disclosure does not show (i) which portions of the polypeptide of SEQ ID NO: 5 are critical to its activity; and (ii) what modifications (e.g., substitutions, deletions or additions) one can make to SEQ ID NO: 4 or 6 will result in a mutant or a fragment with the same functions as that of the polypeptide set forth in SEQ ID NO: 5.

It is unpredictable whether a variant or a homologue would retain the same function as that of the full length of polypeptide of SEQ ID NO: 5 due to lack of sufficient guidance provided in the specification and the teachings in the art on how to use those variants or homologues of the polypeptide of SEQ ID NO: 5. The state of the art (See, e.g., Ngo, et al, *The Protein Folding Problem and Tertiary Structure Prediction*, 1994, Merz, et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495) is such that the relationship between sequence of a protein and its activity is not well understood and is not predictable. Excising out portions of a protein or modifications to a protein, e.g., by substitutions or deletions, would often result in deleterious effects to the overall activity and effectiveness of the protein.

Furthermore, the state of the art is such that determining the specificity of hybridization is empirical by nature and the effect of mismatches is

unpredictable, as taught by Wallace et al. (Methods Enzymol. 152:432-443, 1987) and Sambrook et al. (Molecular Cloning, A Laboratory Manual, 2nd Edition, 1989, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, page 11.47). It is well known in the art that hybridisation yields nucleic acids that are structurally related, but functionally different. Thus, in view of the nature of complexity of the work and unpredictability of the art, it would take undue experimentation for one skilled in the art to make and use the claimed genus of compounds without sufficient guidance, working examples, and knowledge about functions of encompassed nucleic acid molecules structurally related to the nucleic acid sequence encoding the polypeptide of SEQ ID NO: 5.

Accordingly, even if the nucleic acid encoding the polypeptide of SEQ ID NO: 5 were to have a patentable utility, the instant disclosure would not be found to be enabling for the full scope of the invention of claims 38-40. Thus, it would require undue experimentation for one skilled in the art to make and use the claimed invention commensurate in scope with the claims.

Claim Rejections—35 USC §112, 1st paragraph

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 38-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

Claims 38-40 are drawn to a kit comprising a compound which selectively hybridizes to a nucleic acid molecule encoding the amino acid sequence of SEQ ID NO: 5. The claims do not require that the compound possesses any particular conserved structure nor other disclosed distinguishing feature. Thus, the claims are drawn to a genus of compound that is defined only by a recited property: selectively hybridizes to a nucleic acid of claims 23, 24, or 25.

The instant disclosure of two isolated nucleic acids set forth in SEQ ID NO: 4 and SEQ ID NO: 6 that encode a polypeptide of SEQ ID NO: 5 does not adequately support the scope of the claimed genus of compounds. A description of a genus of cDNA may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569,

43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Besides the disclosure of the nucleic acid encoding the polypeptide of SEQ ID NO: 5, the instant disclosure fails to provide sufficient description information, such as definitive structural or functional features of the claimed genus of compounds. There is no description of the conserved regions that are critical to the structure and function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Moreover, the claims encompass virtually any random nucleic acid sequence of any length since claims do not recite specific hybridization conditions and any nucleic acids could hybridize to the recited nucleic acids. Furthermore, the prior art does not provide compensatory structural or correlative teachings to enable one skilled in the art to identify the encompassed nucleic acid molecules as being identical to those instantly claimed.

Due to the breadth of the claimed genus and lack of the definitive structural or functional features of the claimed genus, one skilled in the art would not recognize from the disclosure that the applicant was in possession of the claimed genus. Accordingly, only the isolated nucleic acids of SEQ ID NOS: 4 and 6 and its fragments that are useful for probes, but not the full breadth of the claims meets the written description provision of 35 U.S.C. §112, first paragraph.

Claim Rejections—35 USC § 112, 2nd paragraph

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claim 38-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 38-40 are indefinite because they recite "a compound which selectively hybridize to a nucleic acid molecule...". It is unclear what else besides a nucleic acid is encompassed by the 'compound'.

Claim Rejections—35 USC § 102(b)

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 38-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Hillier et al. (EMBL Database, Accession No. AA292507, May 16, 1997).

Hillier et al. teach a nucleotide sequence with 599 nucleotides, which comprises 512 consecutive nucleotides of SEQ ID NO: 4 (see attached sequence alignment). By its nature, the complimentary sequence of the nucleic acid selectively hybridizes to the nucleic acid molecule of SEQ ID NO:

4. It should be noted that "instructions for use" included in the kit does not constitute the patentable subject matter. Thus, the reference of Hillier et al. meets the limitations of Claims 38-40.

Claim Objections—Minor Informalities

15. Claims 23-40 are objected to because they recite non-elected subject matter (nucleic acid/amino acid sequences). Appropriate correction is required.

Conclusion

16. No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (571) 272-0875. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (571) 272-0829. The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private

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Ruixiang Li

Ruixiang Li, Ph.D.
Examiner
June 8, 2005